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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/620,278	07/15/2003	Barrett R. Harvey	UTXB:715US	4200

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EXAMINER	
FORD, VANESSA L	

ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 12/20/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/620,278	HARVEY ET AL.	
	Examiner	Art Unit	
	Vanessa L. Ford	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 September 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-48* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *7/15/2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *9/23/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

1. This Office Action is responsive to Applicant's amendment and response filed September 17, 2004. Claims 12, 24 and 43 have been amended. Claim 48 has been added. Applicant's submission of Exhibit A-D are acknowledged.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in the prior Office Action.

Rejections Withdrawn

3. In view of Applicant's amendment and response the following rejections are withdrawn:

a) Objection to claim 43, page 2, paragraph 1.

b) Rejection of claims 1-47 under 35 U.S.C. 112, first paragraph, pages 2-16, paragraph 3.

c) Rejection of claims 1 and 43 under 35 U.S.C. 112, second paragraph, page 16, paragraph 5.

d) Rejection of claim 12 under 35 U.S.C. 112, second paragraph, page 16, paragraph 6.

e) Rejection of claims 1-47 under 35 U.S.C. 112, second paragraph, page 17, paragraph 8.

Rejections Maintained

4. The rejection under 35 U.S.C. 112, second paragraph is maintained for claims 1 and 3 the reasons set forth on page 16, paragraph 4 of the previous Office Action.

The rejection was on the grounds that the claims recite the term "capable of". It is unclear as to what the applicant is referring? Thus, the metes and bounds of "capable of" cannot be ascertained. Clarification as to the meaning of this term is required.

Applicant urges that the phrase "capable of" is definite. Applicant refers to the online dictionaries for the meaning of the term. Applicant urges that "capable of" is a readily ascertainable standard well known to those skilled in the art.

Applicant's arguments filed September 17, 2004 have been fully considered but they are not persuasive. "Capable of" is a potential. Does the invention have the recited function or not? It should be remembered that the claims point out and distinctly claims the invention (see MPEP 2172 and 2173).

5. The rejection under 35 U.S.C. 112, second paragraph is maintained for claim 22 the reasons set forth on page 17, paragraph 7 of the previous Office Action.

The rejection was on the grounds that the claim recites the term "small molecule" and " synthetic molecule". It is unclear as to what the applicant is referring? Thus, the metes and bounds of "small molecule" and " synthetic molecule" are not disclosed in the instant specification and therefore cannot be ascertained. Clarification as to the meaning of this terms is required.

Applicant did not respond to this rejection. Therefore, this rejection is maintained.

New Grounds of Rejection

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

6. Claims 1, 4-9, 13-15, 17-24 and 34-35 are rejected under 35 U.S.C. 102(e) as anticipated by Hultgren et al, *(U.S. Patent No. 6,001,823, published December 14, 1999).*

Claims 1, 4-9, 13-15, 17-24 and 34-35 are drawn to a method of obtaining a bacterium comprising a nucleic acid sequence encoding a binding protein having specific affinity for a target ligand comprising the steps of: providing a gram-negative bacterium comprising an inner and outer membrane and periplasm said bacterium expressing a nucleic acid sequence encoding a candidate binding polypeptide wherein the candidate bindng polypeptide is exposed within the periplasm of said bacterium; contacting said bacterium with a labeled ligand under conditions wherein the labeled ligand is capable of contacting the binding polypeptide; and selecting said bacterium based on the presence of said labeled ligand bound to said candidate binding polypeptide.

Hultgren et al teach a method for identifying a potentially therapeutically useful substance capable of interacting with a periplasmic molecular chaperone thereby preventing or inhibiting the interaction between a periplasmic molecular chaperone and a pilus subunit (column 10). Hultgren et al teach that the periplasmic chaperone or analogue thereof is in solubilized form (column 10). Hultgren et al teach that the measurement of the degree of binding can be determined *in vitro* by methods such as microcolormetric, radioimmunoassays and enzyme based assays (column 6). Hultgren et al teach that in instances wherein labeled substances, chaperones or antibodies are used, the label could be a radioactive label, a fluorescent or light absorbing label, an enzyme such as horseradish peroxidase, a ligand such as biotin or any other conventional labeling system known those skilled in the art (column 12). Hultgren et al teach that the binding between chaperones and pilus subunits are obtained by the

interaction between the PapD chaperone in *E. coli.* (column 8). Since the interaction between the chaperones and pilus subunits takes place in the periplasmic space the nucleic acid sequences encoding the chaperones would be inherent in the teachings of the prior art.

Since the Office does not have the facilities for examining and comparing applicant's method with the method of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed method and the method of the prior art (i.e., that the method of the prior art does not possess the same material method steps and parameters of the claimed method). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

7. Claims 1-41 and 43-48 are rejected under 35 U.S.C. 102(b) as anticipated by Iverson et al (*WO 98/49286, published November 5, 1998).*

Claims 1-41 and 43-48 are drawn to a method of obtaining a bacterium comprising a nucleic acid sequence encoding a binding protein having specific affinity for a target ligand comprising the steps of: providing a gram-negative bacterium comprising an inner and outer membrane and periplasm said bacterium expressing a nucleic acid sequence encoding a candidate binding polypeptide wherein the candidate bindng polypeptide is exposed within the periplasm of said bacterium; contacting said bacterium with a labeled ligand under conditions wherein the labeled ligand is capable of contacting the binding

polypeptide; and selecting said bacterium based on the presence of said labeled ligand bound to said candidate binding polypeptide.

Iverson et al teach a method of obtaining a library of vectors that encode a plurality of distinct candidate polypeptides, wherein said vectors provide for the cell surface expression of candidate polypeptides, expressing each of said plurality of candidate polypeptides on the surface f a host cell and selecting a host cell that expresses the desired polypeptide. (see the Abstract and page 123). Iverson et al teach that the "expression construct" is a genetic construct containing a nucleic acid coding for a gene product in which part or all of the nucleic acid is capable of being transcribed. Iverson et al teach that the host cell is a gram-negative bacterium, *E. coli* (claims 2-3, page 123) and that a plurality of DNA segments are incorporated into expression vectors and the vectors express antibodies or antibody fragments on the outer membrane surface of *E. coli* (claim 11, page 124). Iverson et al teach that a targeting sequence has been developed that when it is fused to normally soluble proteins, it can direct soluble proteins to the cell surface (page 22). Iverson et al also teach that the polypeptide is elected from the groups consisting of an antibody or antibody fragment, an enzyme, a cytokine, a transcription factor, a clotting factor, a chelating agent, a hormone and a receptor (claim 4, page 123). Iverson et al teach that the cells displaying antibodies having affinity for a desired analyte are isolated and that identifying the antibody or antibody fragment expressing cells may be accomplished by methods of detecting the presence of the bound detectable label. Iverson et al teach that the labeled ligand can comprise

radioactive, fluorescent, chemiluminescent, electrochemiluminescent, biological or enzymatic tags (page 51). Iverson teach that one aspect of this method is fluorescence activated cell sorting (FACS) and that high affinity clones, the production of soluble antibodies can be achieved easily without the need for further subcloning steps. Iverson et al teach that the clones may be maintained under standard culture conditions (about 24°C) (page 61) and employed to produce the selected antibody and production of antibody is limited only to the scaleup of the cultures (page 48). Iverson et al teach that the cells with the antibody displayed on the surface may themselves be attached to a solid support such as a membrane, dipstick or magnetic beads to further facilitate removal of the cells following the assay (pages 49 and 55). Iverson et al teach that cells were harvested and resuspended in PBS pH 7.4 at a concentration of 10^{10} cell/ml based on the $O.D._{600}$ to form a cell shock and some cells were resuspended in 15 % glycerol /water and stored at 70°C (i.e. hyperosmotic conditions and physical stress) (page 67). Iverson et al also teach that cultures of the invention were cultured at 25oC (sub-physiological temperatures) (page 71).

Since the Office does not have the facilities for examining and comparing applicant's method with the method of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed method and the method of the prior art (i.e., that the method of the prior art does not possess the same material method steps and parameters of the claimed method). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 1-48 are rejected under 35 U.S.C. 103(a) as unpatentable over Iverson et al (*WO 98/49286, published November 5, 1998)* in view of Staudenmaier et al *(Journal of Bacteriology, May 1989, p. 2626-2633).*

Claims 1-48 are drawn to a method of obtaining a bacterium comprising a nucleic acid sequence encoding a binding protein having specific affinity for a target ligand comprising the steps of: providing a gram-negative bacterium comprising an inner and outer membrane and periplasm said bacterium expressing a nucleic acid sequence encoding a candidate binding polypeptide wherein the candidate bindng polypeptide is exposed within the periplasm of said bacterium; contacting said bacterium with a labeled ligand under conditions wherein the labeled ligand is capable of contacting the binding polypeptide; and selecting said bacterium based on the on the presence of said labeled ligand bound to said candidate binding polypeptide, wherein the sequence is an inner membrane lipoprotein or fragment thereof.

Iverson et al teach a method of obtaining a library of vectors that encode a plurality of distinct candidate polypeptides, wherein said vectors provide for the cell surface expression of candidate polypeptides, expressing each of said plurality of candidate polypeptides on the surface of a host cell and selecting a host cell that expresses the desired polypeptide. (see the Abstract and page 123). Iverson et al teach that the "expression construct" is a genetic construct containing a nucleic acid coding for a gene product in which part or all of the nucleic acid is capable of being transcribed. Iverson et al teach that the host cell is a gram-negative bacterium, *E. coli* (claims 2-3, page 123) and that a plurality of DNA segments are incorporated into expression vectors and the vectors express antibodies or antibody fragments on the outer membrane surface of *E. c*oli (claim 11, page 124). Iverson et al teach that a targeting sequence has been developed that when it is fused to normally soluble proteins, it can direct soluble proteins to the cell surface (page 22). Iverson et al also teach that the polypeptide is elected from the groups consisting of an antibody or antibody fragment, an enzyme, a cytokine, a transcription factor, a clotting factor, a chelating agent, a hormone and a receptor (claim 4, page 123). Iverson et al teach that the cells displaying antibodies having affinity for a desired analyte are isolated and that identifying the antibody or antibody fragment expressing cells may be accomplished by methods of detecting the presence of the bound detectable label. Iverson et al teach that the labeled ligand can comprise radioactive, fluorescent, chemiluminescent, electrochemiluminescent, biological or enzymatic tags (page 51). Iverson teach that one aspect of this method is

fluorescence activated cell sorting (FACS) and that high affinity clones, the production of soluble antibodies can be achieved easily without the need for further subcloning steps. Iverson et al teach that the clones may be maintained under standard culture conditions (about 24°C) (page 61) and employed to produce the selected antibody and production of antibody is limited only to the scaleup of the cultures (page 48). Iverson et al teach that the cells with the antibody displayed on the surface may themselves be attached to a solid support such as a membrane, dipstick or magnetic beads to further facilitate removal of the cells following the assay (pages 49 and 55). Iverson et al teach that cells were harvested and resuspended in PBS pH 7.4 at a concentration of 10^{10} cell/ml based on the $O.D._{600}$ to form a cell shock and some cells were resuspended in 15 % glycerol /water and stored at 70°C (i.e. hyperosmotic conditions and physical stress) (page 67). Iverson et al also teach that cultures of the invention were cultured at 25oC (sub-physiological temperatures) (page 71).

Iverson et al do not specially teach the inner membrane lipoproteins FecC or FecD.

Staudenmaier et al teach that the FecBCDE genes region of *E. coli.* Determines a citrate-dependent iron(III) transport system (see the Abstract). Staudenmaier et al teach that locations of the Fec encoded polypeptides suggest a periplasmic-binding-protein-dependent transport mechanism for Iron(III) dicitrate in E. *coli* (see the Title and the Abstract). Staudenmaier et al teach that the FecC and FecD are hydrophobic polypeptides that are localized in the cyctoplasmic membrane (see the Abstract).

It would be *prime facie* obvious at the time the invention was made use FecC or FecD as a an inner membrane lipoprotein in the method of Iverson et al because Iverson et al teach that expression of recombinant proteins are achieved by fusion of segments of lipoproteins (page 14) and Staudenmaier et al teach that locations of the Fec encoded polypeptides suggest a periplasmic-binding-protein-dependent transport mechanism in E. *coli.* It would be expected barring evidence to the contrary that the use of lipoproteins FecC or FecD would be effective transmembrane anchors since that are localized in the cyctoplasmic membrane and are a part of a periplasmic-binding-protein-dependent transport mechanism in E. *coli.*

Status of Claims

9. No claims are allowed.

Conclusion

10. Any inquiry of the general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308–0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Office Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for the Group 1600 is (703) 872-9306.

Any inquiry concerning this communication from the examiner should be directed to Vanessa L. Ford, whose telephone number is (571) 272-0857. The examiner can normally be reached on Monday – Friday from 9:00 AM to 6:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached at (571) 272-0864.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov./>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Vanessa L. Ford
Biotechnology Patent Examiner
December 8, 2004

MARK NAVARRO
PRIMARY EXAMINER